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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,044	07/14/2005	Ralph Biemans	B45313	7576

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
10/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/523,044	BIEMANS ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,14-20,53,59 and 60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,14 16-18,59 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/26/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted on 6/26/08 is made. Claims 1-8, 14, 16-18, 59 and 60 are currently under examination.

Claims 15, 19, 20 and 53 were previously withdrawn from consideration.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quakyi et al (Infect. Immun. 65(5): 1972-9. 1997) in view of Jennings et al (Molecular Microb. Nov. 1995. 18(4): 729-740) in light or Wakarchuk et al (J.Biol.Chem. 1996. 271(32): 19166-19173).

Quakyi et al disclose outer membrane vesicles (blebs) of a mutant Neisseria meningitidis M986-OP-strains, producing a truncated LOS mutant. These truncated LOS in an outer membrane vesicle (bleb) are shown to be less toxic than purified LOS and induce a protective immune response. Methods for obtaining these outer membrane vesicles (blebs) are also taught. See pages 1972-3, last paragraph-page 1973, col. 2 paragraph 1; page 1974-last para.-1978, col. 1, paragraph 1; page 1978, col. 1, para. 4 and column 2, last paragraph, as well as absract).

Quakyi also teaches that a neisserial bleb preparation derived from a nonencapsulated strain is less toxic than the bleb strqain from an encapsulated neisserial strain.

However, Quakyi do not disclose that the mutant Neisseria strain is mutated in LgtB causing permanent dowregulation of the lgtb gene.

Jennings et al teach a neisserial strain having a mutant LgtB gene with a truncated LOS. The mutant was constructed by insertion of a kanamycin antibiotic resistance cassette which inactivates the LgtB gene (see page 733, column 1, paragraph 2-page 734, col. 1, paragraph 1. Warchuk (abstract and page 19167, col. 1, paragraph 2) is cited because it shows the same LGtB 03 strain as taught by Quakyi and teaches that this strain appears to have the L3 LOS immunotype.

Accordingly, it would therefore have been obvious to one of ordinary skill in the art at the time the invention was made to use an LgtB- neisserial strain having a truncated LOS as taught by Jennings et al to produce the blebs taught by Quakyi because Jennings et al teach that such blebs having truncated LOS are less toxic.

3. Claims 4-8, 14-18, 59 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quakyi et al (Infect. Immun. 65(5): 1972-9. 1997) in view of Jennings et al (Molecular Microb. Nov. 1995. 18(4): 729-740) in light or Wakarchuk et al (J.Biol.Chem. 1996. 271(32): 19166-19173), as applied to claims 1-3 above, further in view of Berthet (WO 01/09350) and Gu et al. (infect. Immun. ASM 61(5): 1873-1880. May 1993).

The teachings of Quakyi et al (Infect. Immun. 65(5): 1972-9. 1997) in view of Jennings et al (Molecular Microb. Nov. 1995. 18(4): 729-740) in light or Wakarchuk et al (J.Biol.Chem. 1996. 271(32): 19166-19173) are set forth above; however, the rejection does not teach or

suggest bleb preparations which are genetically engineered to downregulate the expression of functional gene products from other capsular polysaccahride genes.

Berthet et al disclose vaccine compositions comprising non-toxic Gram-negative bleb vaccines, blebs made from *N.meningitidis, M.catarrhalis* and *H.influenzae*, for pediatric use. See abstract. The blebs are modified to have down-regulation of immundominant non-protective antigens, up-regulation of protective antigens and detoxification of the Lipid A moiety of LPS. It is particularly exemplified that *N.meningitidis* B strain lacking capsular polysaccharides may be used to isolate the blebs, e.g., such as the ones taught by Quakyi et al. See claim 14 and page 42 of Berthet. The down-regulation genes include one or more of htrB, msbB and others. See claim 17 and page 23 of the prior art. SiaD is specifically taught as one of the genes to be down-regulated in claim 20. The down-regulated genes also include one or more selected from the group comprising: porA, porB, opA, opC, pilC, FrpB, etc. See claims 15-16 and page 31 of Berthet. The upregulated genes also include one or more of Hsf, Hap, TbpA. See claims 22 and 27 of Berthet. Berthet teach that other antigens may be conjugated to the bleb preparations, including other antigens from *N.meningitidis*, such as meningococcal capsular polysaccharides from the serotypes A, C, Y or W. See claims 36-39.

Since Quakyi teaches that a neisserial bleb preparation derived from a nonencapsulated strain is less toxic than the bleb strain from an encapsulated neisserial strain and Berthet specifically teaches that *N.meningitidis* B strain lacking capsular polysaccharides may be used to isolate the blebs (see claim 14 and page 42 of Berthet) and Jennings et al teach a neisserial strain having a mutant LgtB gene with a truncated LOS are less toxic, it would have been prima facie obvious to one of ordinary skill in the art to combine a mutation of LgtB- and downregulation of

a capsular polysaccharide gene in order to get a nessieral strain from which to use blebs as vaccine with lower toxicity. The blebs in Berthet are modified to have down-regulation of immundominant non-protective antigens, up-regulation of protective antigens and detoxification of the Lipid A moiety of LPS. The down-regulation genes include one or more of htrB, msbB and others. See claim 17 and page 23 of the prior art. SiaD is specifically taught as one of the genes to be down-regulated in claim 20. The down-regulated genes also include one or more selected from the group comprising: porA, porB, opA, opC, pilC, FrpB, etc. See claims 15-16 and page 31 of Berthet. The upregulated genes also include one or more of Hsf, Hap, TbpA. See claims 22 and 27 of Berthet. Berthet teach that other antigens may be conjugated to the bleb preparations, including other antigens from *N.meningitidis*, such as meningococcal capsular polysaccharides from the serotypes A, C, Y or W. Accordingly, one of ordinary skill in the art with the information available at the time the invention was made would have been motivated to use a bleb preparation from Lgtb mutant with a L3 LOS immunotype, especially given the fact that Gu et al specifically teach that the predominant LOS type in the group B disease strains is L3. See column 7, lines 42-43.

Although Berthet teach that other antigens may be conjugated to the bleb preparations, including other antigens from *N.meningitidis*, they do not particularly exemplify the use of LOS of any immunotype, nor do they exemplify that the strain used to make their blebs possessed an L3 LOS immunotype naturally.

Gu et al teach conjugate vaccines comprising detoxified LOS linked to immunogenic carriers for use as vaccines against N.meningitidis. Gu teach that the LOS from N.meningitidis have 12 immunotypes, L1-L12. They teach that L1 to L8 are indentified within groups B and C

meningococci. Gu et al specifically teach that the predominant LOS type in the group B disease strains is L3. See column 7, lines 42-43. Additionally, as stated above, Warchuk (abstract and page 19167, col. 1, paragraph 2) is cited because it shows the same LGtB 03 strain as taught by Quakyi and teaches that this strain appears to have the L3 LOS immunotype. Gu et al teach that their LOS may be covalently linked to an immunogenic carrier and may be composed of detoxified LOS from different strains and/or immunotypes of N.meningitidis. See Columns 1 and 2. It is taught that LOS may be directly covalently bound to the protein or carrier, for example, by using the cross linking reagent glutaraldehyde. See column 4, lines 60-65. It is taught that linkers may also be used. Blebs were well known in the art as immunogenic carriers containing T-helper epitopes which could be used in multivalent vaccines, as evidenced by Berthet. One of ordinary skill would not want to use a bleb preparation from a toxic strain as it could not be safely used in immunization procedures. The use of adjuvants are taught in both references. The lgtB mutant strain taught by Jennings would inherently possess an intermediate LOS structure in which the terminal galactose residue and sialic acid are absent.

Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645

10/23/08